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(57) Abstract

A medicament containing, separately or together, (A) formoterol or a pharmaceutically acceptable salt thereof or a solvate of formoterol or said salt and (B) a tiotropium salt of a pharmaceutically acceptable acid, for simultaneous, sequential or separate administration in the treatment of an inflammatory or obstructive airways disease.

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Combinations of Formoterol and a Tiotropium Salt

This invention relates to combinations of formoterol and a tiotropium salt and their use for the treatment of inflammatory or obstructive airways diseases.

Formoterol,N-[2-hydroxy-5-(1-hydroxy-2-((2-(4-methoxyphenyl)-1-methylethyl)amino)-ethyl)phenyl]formamide, particularly in the form of its fumarate salt, is a bronchodilator used in the treatment of inflammatory or obstructive airways diseases. Use of tiotropium bromide, (1α,2β,5α,7β)-7-((hydroxydi-2-thienylacetyl)oxy)-9,9-dimethyl-3-oxa-9-azonia-tricyclo(3.3.1.$0^{2,4}$)-nonane bromide, in the treatment of chronic obstructive bronchitis is described in US5610163. It has now surprisingly been found that a significant unexpected therapeutic benefit, particularly a synergistic therapeutic benefit, in the treatment of inflammatory or obstructive airways diseases can be obtained by combination therapy using formoterol, or a salt or solvate thereof, and a tiotropium salt. For instance, it is possible using this combination therapy to reduce the dosages required for a given therapeutic effect considerably compared with those required using treatment with formoterol or a tiotropium salt alone, thereby minimising possibly undesirable side effects.

In a further aspect, this combination therapy exhibits both a fast onset of action and a long duration of action, so that patients feel a rapid improvement in their condition and, in view of the long duration of action, a reduced need for short-acting rescue medicaments, such as salbutamol or terbutaline. Surprisingly this effect is exhibited even when the two drugs are administered at the same time, i.e. in a composition containing both drugs or sequentially, so that medicaments of the invention facilitate the treatment of inflammatory or obstructive airways diseases with a medicament which need be administered only once a day. Where necessary, medicaments of the invention can be used on demand in rescue treatment of obstructive or inflammatory airways diseases, so that they facilitate treatment of such diseases with a single medicament.

In one aspect, the present invention provides a medicament containing, separately or together, (A) formoterol or a pharmaceutically acceptable salt thereof or a solvate of formoterol or said salt and (B) a tiotropium salt of a pharmaceutically acceptable acid, for simultaneous, sequential or separate administration in the treatment of an inflammatory or obstructive airways disease.

In another aspect, the present invention provides a method of treating an inflammatory or obstructive airways disease which c mprises administering to a subject in need of such treatment effective amounts of (A) as hereinbefore defined and (B) as hereinbefore defined.

In a further aspect, the present invention provides a phamaceutical composition comprising a mixture of effective amounts of (A) as hereinbefore defined and (B) as hereinbefore defined, optionally together with a pharmaceutically acceptable carrier.

The present invention also provides (A) and (B) as hereinbefore defined for use in combination therapy by simultaneous, sequential or separate administration in the treatment of an inflammatory or obstructive airways disease.

The invention further provides the use of (A) as hereinbefore defined or (B) as hereinbefore defined in the preparation of a medicament for combination therapy by simultaneous, sequential or separate administration of (A) and (B) in the treatment of an inflammatory or obstructive airways disease.

The present invention still further provides the use of (A) and (B) as hereinbefore defined for the preparation of a medicament for combination therapy by simultaneous, sequential or separate administration in the treatment of an inflammatory or obstructive airways disease.

Pharmaceutically acceptable salts of formoterol include, for example, salts of inorganic acids such as hydrochloric, hydrobromic, sulfuric and phosphoric acids, and organic acids such as fumaric, maleic, acetic, lactic, citric, tartaric, ascorbic, succinic, glutaric, gluconic, tricarballylic, oleic, benzoic, p-methoxybenzoic, salicylic, o- and p-hydroxybenzoic, p-chlorobenzoic, methanesulfonic, p-toluenesulfonic and 3-hydroxy-2-naphthalene carboxylic acids.

Component (A) may be in any isomeric form or mixture of isomeric forms, for example a pure enantiomer, a mixture of enantiomers, a racemate or a mixture thereof. It may be in the form of a solvate, for example a hydrate, thereof, for example as described in US3994974 or US5684199, and may be present in a particular crystalline form, for example as described in WO95/05805. Preferably, component (A) is formoterol fumarate, especially in the form of the dihydrate.

The tiotropium salt (B) is preferably tiotropium methanesulfonate or , especially, tiotropium bromide,(1α,2β,4β,5α,7β)-7-((hydroxydi-2-thienylacetyl)oxy)-9,9-dimethyl-3-oxa-9-azoniatricyclo(3.3.1.$0^{2,4}$)-nonane bromide, the preparati n of which is described in US5610163.

Administration of the medicament or pharmaceutical composition as hereinbefore described, i.e. with (A) and (B) in admixture or separate, is preferably by inhalation, i.e. (A) and (B) or the mixture thereof are in inhalable form. The inhalable form of the medicament i.e. of (A) and/or (B) may be, for example, an atomizable composition such as an aerosol comprising the active ingredient, i.e. (A) and (B) separately or in admixture, in solution or dispersion in a propellant, or a nebulizable composition comprising a dispersion of the active ingredient in an aqueous, organic or aqueous/organic medium. For example, the inhalable form of the medicament may be an aerosol comprising a mixture of (A) and (B) in solution or dispersion in a propellant, or a combination of an aerosol containing (A) in solution or dispersion in a propellant with an aerosol containing (B) in solution or dispersion in a propellant. In another example, the inhalable form is a nebulizable composition comprising a dispersion of (A) and (B) in an aqueous, organic or aqueous/organic medium, or a combination of a dispersion of (A) in such a medium with a dispersion of (B) in such a medium.

An aerosol composition suitable for use as the inhalable form of the medicament may comprise the active ingredient in solution or dispersion in a propellant, which may be chosen from any of the propellants known in the art. Suitable such propellants include hydrocarbons such as n-propane, n-butane or isobutane or mixtures of two or more such hydrocarbons, and halogen-substituted hydrocarbons, for example fluorine-substituted methanes, ethanes, propanes, butanes, cyclopropanes or cyclobutanes, particularly 1,1,1,2-tetrafluoroethane (HFA134a) and 1,1,1,2,3,3,3-heptafluoropropane (HFA227), or mixtures of two or more such halogen-substituted hydrocarbons. Where the active ingredient is present in suspension in the propellant, i.e. where it is present in particulate form dispersed in the propellant, the aerosol composition may also contain a lubricant and a surfactant, which may be chosen from those lubricants and surfactants known in the art. Other suitable aerosol compositions include surfactant-free or substantially surfactant-free aerosol compositions. The aerosol composition may contain up to about 5% by weight, for example 0.002 to 5%, 0.01 to 3%, 0.015 to 2%, 0.1 to 2%, 0.5 to 2% or 0.5 to 1%, by weight of the active ingredient, based on the weight of the propellant. Where present, the lubricant and surfactant may be in an amount up to 5% and 0.5% respectively by

weight of the aerosol composition. The aerosol composition may also contain a co-solvent such as ethanol in an amount up to 30% by weight of the composition, particularly for administration from a pressurised metered dose inhalation device.

In another embodiment of the invention, the inhalable form is a dry powder, i.e. (A) and/or (B) are present in a dry powder comprising finely divided (A) and/or (B) optionally together with a finely divided pharmaceutically acceptable carrier, which is preferably present and may be chosen from materials known as carriers in dry powder inhalation compositions, for example saccharides, including monosaccharides, disaccharides, polysaccharides and sugar alcohols such as arabinose, glucose, fructose, ribose, mannose, sucrose, trehalose, lactose, maltose, starches, dextran or mannitol. An especially preferred carrier is lactose. The dry powder may be in capsules of gelatin or plastic, or in blisters, for use in a dry powder inhalation device, preferably in dosage units of 1 μg to 140 μg of the active ingredient. Alternatively, the dry powder may be contained as a reservoir in a multi-dose dry powder inhalation device.

In the finely divided particulate form of the medicament, and in the aerosol composition where the active ingredient is present in particulate form, the active ingredient may have an average particle diameter of up to about 10 μm, for example 0.1 to 5 μm, preferably 1 to 5 μm. The finely divided carrier, where present, generally has a maximum particle diameter up to 300μm, preferably up to 212 μm and conveniently has a mean particle diameter of 40 to 100μm, preferably 50 to 75 μm. The particle size of the active ingredient, and that of the carrier where present in dry powder compositions, can be reduced to the desired level by conventional methods, for example by grinding in an air-jet mill, ball mill or vibrator mill, microprecipitation, spray-drying, lyophilisation or recrystallisation from supercritical media.

The inhalable medicament may be administered using an inhalation device suitable for the inhalable form, such devices being well known in the art. Accordingly, the invention also provides a pharmaceutical product comprising a medicament or pharmaceutical composition as hereinbefore described in inhalable form as hereinbefore described in association with one or more inhalation devices. In a further aspect, the invention provides an inhalation device, or a pack of two or more inhalation devices, containing a medicament or pharmaceutical composition as hereinbefore described in inhalable form as hereinbefore described.

Where the inhalable f rm of the active ingredient is an aerosol composition, the inhalation device may be an aerosol vial provided with a valve adapted to deliver a metered dose, such as 10 to 100 µl, e.g. 25 to 50 µl, of the c mposition, i.e. a device known as a metered dose inhaler. Suitable such aerosol vials and procedures for containing within them aerosol compositions under pressure are well known to those skilled in the art f inhalation therapy. For example, an aerosol composition may be administered from a coated can, for example as described in EP-A-0642992. Where the inhalable form of the active ingredient is a nebulizable aqueous, organic or aqueous/organic dispersion, the inhalation device may be a known nebulizer, for example a conventional pneumatic nebulizer such as an airjet nebulizer, or an ultrasonic nebulizer, which may contain, for example, from 1 to 50 ml, commonly 1 to 10 ml, of the dispersion; or a hand-held nebulizer, for example an electronically controlled device such as an AERx (ex Aradigm, US) or a mechanical device such as a RESPIMAT (Boehringer Ingelheim) nebulizer which allows much smaller nebulized volumes, e.g. 10 to 100 µl, than conventional nebulizers. Where the inhalable form of the active ingredient is the finely divided particulate form, the inhalation device may be, for example, a dry powder inhalation device adapted to deliver dry powder from a capsule or blister containing dry powder comprising a dosage unit of (A) and/or (B), or a multidose dry powder inhalation (MDPI) device adapted to deliver, for example, 5-25 mg of dry powder comprising a dosage unit of (A) and/or (B) per actuation. Suitable such dry powder inhalation devices are well known. For example, a suitable device for delivery of dry powder in encapsulated form is that described in US3991761, while a suitable MDPI device is that described in WO97/20589.

The medicament of the invention is preferably a pharmaceutical composition comprising a mixture of (A) as hereinbefore defined and (B) as hereinbefore defined, preferably together with a pharmaceutically acceptable carrier as hereinbefore described.

The weight ratio of formoterol, or salt or solvate thereof, to tiotropium salt may be, in general, from 72:1 to 1:160, for example from 72:1 to 1:120, from 72:1 to 1:80, from 60:1 to 1:80, from 60:1 to 1:70, from 50:1 to 1:60, from 60:1 to 1:50, from 50:1 to 1:50, from 60:1 to 1:40, from 50:1 to 1:40, from 50:1 to 1:30, from 50:1 to 1:20, from 50:1 to 1:30, from 50:1 to 1:20, from 50:1 to 1:10, from 40:1 to 1:20, from 40:1 to 1:10, from 30:1 to 1:20, from 30:1 to 1:10, from 20:1 to 1:20, from 20:1 to 1:10, from 20:1 to 1:5, from 16:1 to 1:4, from 10:1 to 1:5, from 6:1 to 1:4, or from 4:1 to 1:3. More usually, this ratio is from 3:1 to 1:3, for example from 2.5:1 to 1:2, from 2:1 to 1:2, from 1.5:1 to 1:1.5, or from 1.5:1 to 1:1.2. The two drugs may be administered separately in the same

ratio. Specific examples of this ratio include 3:1, 2.9:1, 2.8:1, 2.7:1. 2.6:1. 2.5:1. 2.4:1, 2.3:1, 2.2:1, 2.1:1, 2:1,1.9:1, 1.8:1, 1.7:1, 1.6:1, 1.5:1, 1.4:1, 1.3:1, 1.2:1, 1.1:1, 1:1, 1:1.1, 1:1.2, 1:1.3, 1:1.4, 1:1.5, 1:1.6, 1:1.7, 1:1.8, 1:1.9 and 1:2. The above weight ratios apply particularly where (A) is formoterol fumarate dihydrate and (B) is tiotropium bromide. Thus, since the molecular weights of formoterol fumarate dihydrate and tiotropium bromide are 840.9 and 472.4 respectively, the corresponding molar ratios, which apply to any forms of (A) and (B), can be readily calculated. For instance, the above weight ratios of 60:1 and 1:80 correspond to molar ratios of 33.7:1 and 1:142.3 respectively.

A suitable daily dose of formoterol, or salt or solvate thereof, particularly as formoterol fumarate dihydrate, for inhalation may be from 1 to 72 μg, for example from 1 to 60 μg, generally from 3 to 50 μg, preferably from 6 to 48 μg, for instance from 6 to 24 μg. A suitable daily dose of tiotropium salt, particularly as tiotropium bromide, for inhalation may be from 1 to 160 μg, for example from 1 to 120 μg, from 1 to 80μg, from 1 to 70μg, from 1 to 60 μg, from 1 to 50 μg, from 1 to 40 μg, from 1 to 25 μg, preferably from 3 t 36 μg, for instance from 9 to 36 μg. The precise dose used will of course depend on the condition to be treated, the patient and the efficiency of the inhalation device. The unit doses of (A) and (B) and their frequency of administration may be chosen accordingly. A suitable unit dose of formoterol component (A), particularly as formoterol fumarate dihydrate, may be from 1 to 72 μg, for example from 1 to 60 μg, generally from 3 to 48 μg, preferably from 6 to 36 μg, especially from 12 to 24 μg. A suitable unit dose of tiotropium salt (B), particularly as tiotropium bromide, may be from 1 μg to 80 μg, for example from 1 μg to 50 μg, preferably from 3 μg to 36 μg, especially from 9 to 36 μg. These unit doses may suitably be administered once or twice daily in accordance with the suitable daily dose mentioned hereinbefore. For on demand usage, unit doses of 6μg to 12 μg of (A) and 3μg to 36μg of (B) are preferred.

In one preferred embodiment of the invention, when the medicament of the invention is a pharmaceutical composition which is a dry powder in capsules containing a unit dose of (A) and (B), for example for inhalation from a single capsule inhaler, the capsules may suitably contain, where (A) is formoterol fumarate dihydrate, and (B) is tiotropium bromide, from 3 μg to 36 μg of (A), preferably from 6 μg to 24 μg of (A), especially from 12 μg to 24 μg of (A), and from 3 μg to 80 μg of (B), preferably from 5 μg to 50 μg of (B), especially from 9 to 36 μg of (B), together with a pharmaceutically acceptable carrier as hereinbefore described in an amount to bring the total weight of dry powder per capsule to

between 5 mg and 50mg, for example 5mg, 10mg, 15mg, 20mg, 25mg, 30mg, 35mg, 40mg, 45mg or 50mg, preferably 20 to 25 mg, especially 25 mg.

In another preferred embodiment of the invention, the medicament of the invention is a pharmaceutical composition which is a dry powder for administration from a reservoir of a multi-dose dry powder inhaler adapted to deliver 3mg to 25mg of powder containing a unit dose of (A) and (B) per actuation, for example, where (A) is formoterol fumarate dihydrate, and (B) is tiotropium bromide, a powder comprising, by weight, 3 to 36 parts, preferably 6 to 24 parts, especially 12 to 24 parts of (A); 3 to 80 parts, preferably 5 to 50 parts, especially 9 to 36 parts of (B); and 2884 to 24994 parts, preferably 4884 to 14994 parts, especially 4884 to 9994 parts of a pharmaceutically acceptable carrier as hereinbefore described.

In accordance with the above, the invention also provides a pharmaceutical kit comprising (A) and (B) as hereinbefore defined in separate unit dosage forms, said forms being suitable for administration of (A) and (B) in effective amounts. Such a kit suitably further comprises one or more inhalation devices for administration of (A) and (B). For example, the kit may comprise one or more dry powder inhalation devices adapted to deliver dry powder from a capsule, together with capsules containing a dry powder comprising a dosage unit of (A) and capsules containing a dry powder comprising a dosage unit of (B). In another example, the kit may comprise a multidose dry powder inhalation device containing in the reservoir thereof a dry powder comprising (A) and a multidose dry powder inhalaiton device containing in the reservoir thereof a dry powder comprising (B). In a further example, the kit may comprise a metered dose inhaler containing an aerosol comprising comprising (A) in a propellant and a metered dose inhaler containing an aerosol comprising (B) in a propellant.

Treatment of inflammatory or obstructive airways diseases in accordance with the invention may be symptomatic or prophylactic treatment. Inflammatory or obstructive airways diseases to which the present invention is applicable include asthma of whatever type or genesis including both intrinsic (non-allergic) asthma and extrinsic (allergic) asthma. Treatment of asthma is also to be understood as embracing treatment of subjects, e.g. of less than 4 or 5 years of age, exhibiting wheezing symptoms and diagnosed or diagnosable as "wheezy infants", an established patient category of major medical concern and now often identified as incipient or early-phase asthmatics. (For convenience this particular asthmatic condition is referred to as "wheezy-infant syndrome".)

Prophylactic efficacy in the treatment of asthma will be evidenced by reduced frequency or severity of symptomatic attack, e.g. of acute asthmatic or bronchoconstrictor attack, improvement in lung function or improved airways hyperreactivity. It may further be evidenced by reduced requirement for other, symptomatic therapy, i.e. therapy for or intended to restrict or abort symptomatic attack when it occurs, for example anti-inflammatory (e.g. corticosteroid) or bronchodilatory. Prophylactic benefit in asthma may in particular be apparent in subjects prone to "morning dipping". "Morning dipping" is a recognised asthmatic syndrome, common to a substantial percentage of asthmatics and characterised by asthma attack, e.g. between the hours of about 4 to 6 am, i.e. at a time normally substantially distant form any previously administered symptomatic asthma therapy.

Other inflammatory or obstructive airways diseases and conditions to which the present invention is applicable include acute lung injury (ALI), acute respiratory distress syndrome (ARDS), chronic obstructive pulmonary, airways or lung disease (COPD, COAD or COLD), including chronic bronchitis and emphysema, bronchiectasis and exacerbation of airways hyperreactivity consequent to other drug therapy, in particular other inhaled drug therapy. Further inflammatory or obstructive airways diseases to which the present invention is applicable include pneumoconiosis (an inflammatory, commonly occupational, disease of the lungs, frequently accompanied by airways obstruction, whether chronic or acute, and occasioned by repeated inhalation of dusts) of whatever type or genesis, including, for example, aluminosis, anthracosis, asbestosis, chalicosis, ptilosis, siderosis, silicosis, tabacosis and byssinosis.

The invention is illustrated by the following Examples, in which parts are by weight unless stated otherwise.

Example 1 - Aerosol Composition for Metered Dose Inhaler

Ingredient	% by weight
Formoterol fumarate dihydrate	0.01
Tiotropium bromide	0.01
Ethanol (absolute)	2.50
HFA 227	60.92
HFA134a	36.56

Example 2 - Dry Powder

Ingredient	% by weight
Formoterol fumarate dihydrate	0.05
Tiotropium bromide	0.05
Lactose monohydrate	99.90

Example 3

A dry powder suitable for delivery from the reservoir of the multi-dose inhaler described in WO97/20589 is prepared by mixing 12 parts of formoterol fumarate dihydrate which has been ground to a mean particle diameter of 1-5μm in an air-jet mill, 18 parts of tiotropium bromide which has been similarly ground to a mean particle diameter of 1-5μm and 4970 parts of lactose monohydrate having a particle diameter below 212μm.

Examples 4 - 92

Example 3 is repeated, but using the amounts of the ingredients shown in the table below in place of the amounts used in that Example :

Example	Formoterol Fumarate Dihydrate (Parts)	Tiotropium Bromide (Parts)	Lactose Monohydrate (Parts)
4	12	3	4985
5	12	9	4979
6	12	36	4952
7	12	80	4908
8	6	3	4991
9	6	9	4985
10	6	18	4976
11	6	36	4958
12	6	80	4914
13	18	3	4979
14	18	9	4973
15	18	18	4964

16	18	36	4946
17	18	80	4902
18	24	3	4973
19	24	9	4967
20	24	18	4958
21	24	36	4940
22	24	80	4896
23	30	3	4967
24	30	9	4961
25	30	18	4952
26	30	36	4934
27	30	80	4890
28	36	3	4961
29	36	9	4955
30	36	18	4946
31	36	36	4928
32	36	80	4884
33	6	3	9991
34	6	9	9985
35	6	18	9976
36	6	36	9958
37	6	80	9914
38	12	3	9985
39	12	9	9979
40	12	18	9970
41	12	36	9952
42	12	80	9908
43	18	3	9979
44	18	9	9973
45	18	18	9964
46	18	36	9946
47	18	80	9902
48	24	3	9973
49	24	9	9967
50	24	18	9958

51	24	36	9940
52	24	80	9896
53	30	3	9967
54	30	9	9961
55	30	18	9952
56	30	36	9934
57	30	80	9890
58	36	3	9961
59	36	9	9955
60	36	18	9946
61	36	36	9928
62	36	80	9884
63	6	3	14991
64	6	9	14985
65	6	18	14976
66	6	36	14958
67	6	80	14914
68	12	3	14985
69	12	9	14979
70	12	18	14970
71	12	36	14952
72	12	80	14908
73	18	3	14979
74	18	9	14973
75	18	18	14964
76	18	36	14946
77	18	80	14902
78	24	3	14973
79	24	9	14967
80	24	18	14958
81	24	36	14940
82	24	80	14896
83	30	3	14967
84	30	9	14961
85	30	18	14952

86	30	36	14934
87	30	80	14890
88	36	3	14961
89	36	9	14955
90	36	18	14946
91	36	36	14928
92	36	80	14884

Example 93

Gelatin capsules suitable for use in a capsule inhaler such as that described in US3991761 are prepared, each capsule containing a dry powder obtained by mixing 12μg of formoterol fumarate dihydrate which has been ground to a mean particle diameter of 1 to 5μm in an air jet mill, 18μg of tiotropium bromide which has been similarly ground to a mean particle diameter of 1 to 5μm and 24970μg of lactose monohydrate having a particle diameter below 212μm.

Examples 94 - 152

Example 93 is repeated, but using the amounts of the ingredients shown in the table below in place of the amounts used in that Example :

Example	Formoterol Fumarate Dihydrate (Parts)	Tiotropium Bromide (Parts)	Lactose Monohydrate (Parts)
94	12	3	24985
95	12	9	24979
96	12	36	24952
97	12	80	24908
98	6	3	24991
99	6	9	24985
100	6	18	24976
101	6	36	24958
102	6	80	24914
103	18	3	24979
104	18	9	24973

105	18	18	24964
106	18	36	24946
107	18	80	24902
108	24	3	24973
109	24	9	24967
110	24	18	24958
111	24	36	24940
112	24	80	24896
113	30	3	24967
114	30	9	24961
115	30	18	24952
116	30	36	24934
117	30	80	24890
118	36	3	24961
119	36	9	24955
120	36	18	24946
121	36	36	24928
122	36	80	24884
123	6	3	19991
124	6	9	19985
125	6	18	19976
126	6	36	19958
127	6	80	19914
128	12	3	19985
129	12	9	19979
130	12	18	19970
131	12	36	19952
132	12	80	19908
133	18	3	19979
134	18	9	19973
135	18	18	19964
136	18	36	19946
137	18	80	19902
138	24	3	19973
139	24	9	19967

140	24	18	19958
141	24	36	19940
142	24	80	19896
143	30	3	19967
144	30	9	19961
145	30	18	19952
146	30	36	19934
147	30	80	19890
148	36	3	19961
149	36	9	19955
150	36	18	19946
151	36	36	19928
152	36	80	19884

Examples 153 - 216

Example 3 is repeated, but using the amounts of the ingredients shown in the table below in place of the amounts used in that Example:

Example	Formoterol Fumarate Dihydrate (Parts)	Tiotropium Bromide (Parts)	Lactose Monohydrate (Parts)
153	6	3	2991
154	6	9	2985
155	6	18	2976
156	6	25	2969
157	6	36	2958
158	6	80	2914
159	12	3	2985
160	12	9	2979
161	12	18	2970
162	12	25	2963
163	12	36	2952
164	12	45	2943
165	12	60	2928
166	12	72	2916

167	12	80	2908
168	24	3	2973
169	24	9	2967
170	24	18	2958
171	24	25	2951
172	24	36	2940
173	24	45	2931
174	24	60	2916
175	24	72	2904
176	24	80	2896
177	6	25	4969
178	6	45	4949
179	6	60	4934
180	6	72	4922
181	12	25	4963
182	12	45	4943
183	12	60	4928
184	12	72	4916
185	24	25	4951
186	24	45	4931
187	24	60	4916
188	24	72	4904
189	6	25	9969
190	6	45	9949
191	6	60	9934
192	6	72	9922
193	12	25	9963
194	12	45	9943
195	12	60	9928
196	12	72	9916
197	24	25	9951
198	24	45	9931
199	24	60	9916
200	24	72	9904
201	6	25	14969

202	6	45	14949
203	6	60	14934
204	6	72	14922
205	12	25	14963
206	12	45	14943
207	12	60	14928
208	12	72	14916
209	24	25	14951
210	24	45	14931
211	24	60	14916
212	24	72	14904
213	24	90	14886
214	24	108	14868
215	24	135	14841
216	24	160	14816

Examples 217 - 256

Example 93 is repeated, but using the amounts of the ingredients shown in the table below in place of the amounts used in that Example:

Example	Formoterol Fumarate Dihydrate (µg)	Tiotropium Bromide (µg)	Lactose Monohydrate (µg)
217	6	3	14991
218	6	9	14985
219	6	18	14976
220	6	25	14969
221	6	36	14958
222	6	45	14949
223	6	60	14934
224	6	72	14922
225	6	80	14914
226	12	3	14985
227	12	9	14979
228	12	18	14970

229	12	25	14963
230	12	36	14952
231	12	45	14943
232	12	60	14928
233	12	72	14916
234	12	80	14908
235	12	160	14828
236	24	3	14973
237	24	9	14967
238	24	18	14958
239	24	25	14951
240	24	36	14940
241	24	45	14931
242	24	80	14896
243	6	3	9991
244	6	9	9985
245	6	18	9976
246	6	25	9969
247	6	36	9958
248	6	45	9949
249	6	80	9914
250	12	3	9985
251	12	9	9979
252	12	18	9970
253	12	25	9963
254	12	36	9952
255	12	45	9943
256	12	80	9908

Claims

1. A medicament containing, separately r together, (A) formoterol or a pharmaceutically acceptable salt thereof or a solvate of formoterol or said salt and (B) a tiotropium salt of a pharmaceutically acceptable acid, for simultaneous, sequential or separate administration in the treatment of an inflammatory or obstructive airways disease.

2. A medicament according to claim 1 which is a phamaceutical composition comprising a mixture of effective amounts of (A) and (B), optionally together with a pharmaceutically acceptable carrier.

3. A medicament according to claim 1 or 2, in which (A) is formoterol fumarate.

4. A medicament according to claim 3, in which formoterol fumarate is in the form of the dihydrate thereof.

5. A medicament according to any one of claims 1 to 4, in which (B) is tiotropium bromide.

6. A medicament according any one of claims 1 to 5, which is in inhalable form.

7. A medicament according to claim 6, in which (A) and/or (B) are present in an atomizable composition.

8. A medicament according to claim 7, in which the inhalable form is an aerosol comprising a mixture of (A) and (B) in solution or dispersion in a propellant, or a combination of an aerosol containing (A) in solution or dispersion in a propellant with an aerosol containing (B) in solution or dispersion in a propellant.

9. A medicament according to claim 7, in which the inhalable form is a nebulizable composition comprising a dispersion of (A) and (B) in an aqueous, organic or aqueous/organic medium or a combination of a dispersion of (A) in said medium with a dispersion of (B) in said medium.

10. A medicament according to claim 6, in which (A) and/or (B) are present in a dry powder comprising finely divided (A) and/or (B) optionally together with a pharmaceutically acceptable carrier in finely divided form.

11. A medicament according to claim 10, in which the carrier is present and is a saccharide.

12. A medicament according to claim 11, in which the carrier is lactose.

13. A medicament according to any one of claims 10 to 12, in which (A) and/or (B) has an average particle diameter up to 10 μm.

14. A medicament according to any one of the preceding claims, in which the weight ratio of (A) to (B) is from 72:1 to 1:160.

15. A medicament according to claim 14, in which said ratio is from 60:1 to 1:80.

16. A medicament according to claim 15, in which said ratio is from 3:1 to 1:3.

17. A medicament according to claim 2, which is a dry powder in a capsule, the capsule containing from 3 to 36 μg of (A) as formoterol fumarate dihydrate, from 3 to 80 μg of (B) as tiotropium bromide and a pharmaceutically acceptable carrier in an amount to bring the total weight of dry powder per capsule to betwen 5mg and 50 mg.

18. A medicament according to claim 2, which is a dry powder comprising, by weight, 3 to 36 parts of (A) as formoterol fumarate dihydrate, 3 to 80 parts of (B) as tiotropium bromide and 2884 to 24994 parts of a pharmaceutically acceptable carrier.

19. The use of (A) as defined in any one of claims 1, 3 and 4 or (B) as defined in claim 1 or 5 in the preparation of a medicament for combination therapy by simultaneous, sequential or separate administration of (A) and (B) in the treatment of an inflammatory or obstructive airways disease.

20. The use of (A) as defined in claim 1, 3 or 4 and (B) as defined in claim 1 or 5 for the preparation of a medicament for combination therapy by simultaneous, sequential or separate administration in the treatment of an inflammatory or obstructive airways disease.

21. A pharmaceutical kit comprising (A) as defined in claim 1, 3 or 4 and (B) as defined in claim 1 or 5 in separate unit dosage forms, said forms being suitable for administration of (A) and (B) in effective amounts, together with one or more inhalation devices for administration of (A) and (B).

22. A method of treating an inflammatory or obstructive airways disease which comprises administering to a subject in need of such treatment effective amounts of (A) as defined in claim 1, 3 or 4 and (B) as defined in claim 1 or 5.

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/EP 00/00958

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/135 A61K31/46 A61P11/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	WO 00 16814 A (AEROPHARM TECHNOLOGY INC) 30 March 2000 (2000-03-30) claim 3	1-22
E	DE 198 47 970 A (BOEHRINGER INGELHEIM PHARMA) 20 April 2000 (2000-04-20) page 3, line 15-30	1-22
E	WO 00 07567 A (HERZOG KURT ;JAGO RES AG (CH); KRAUS HOLGER (CH); MUELLER WALZ RUD) 17 February 2000 (2000-02-17) claims 8,10	1-22
Y	WO 95 05805 A (ASTRA AB ;BRIGGNER LARS ERIK (SE); TROFAST EVA ANN CHRISTIN (SE)) 2 March 1995 (1995-03-02) page 7, line 33-37; examples 2,3,6	1-22

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
30 May 2000	07/06/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Gonzalez Ramon, N

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INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/EP 00/00958

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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P,Y	LECKIE M.J. ET AL: "Novel therapy for COPD." EXPERT OPINION ON INVESTIGATIONAL DRUGS, (2000) 9/1 (3-23). , XP000911149 page 9, column 1; table 1	1-22

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INTERNATIONAL SEARCH REPORT

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